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The Life Cycle Of A Retrovirus

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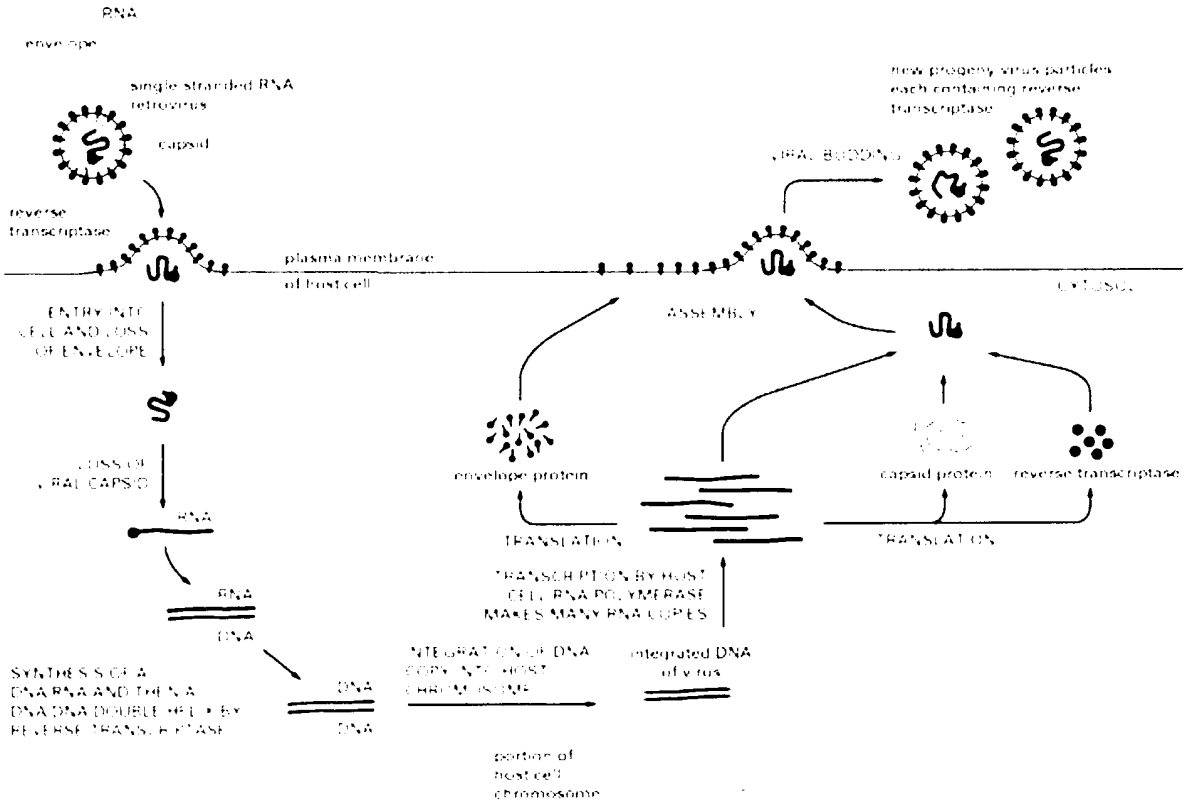

Legend:

The typical retrovirus genome consists of a single-stranded RNA of about 8500 nucleotides. The enzyme reverse transcriptase is a multifunctional enzyme that first makes a DNA copy of the viral RNA molecule. It then acts as a nuclease to remove the RNA, and then makes a second DNA strand, generating a double-stranded DNA copy of the RNA genome. The integration of this DNA into the host chromosome, catalyzed by a viral protein called integrase, is required for the synthesis of new viral RNA molecules by the host cell RNA polymerase. Retroviruses are examples of enveloped viruses, in which the protein shell is further enclosed by an outer lipid bilayer membrane. The envelope contains proteins that enable the virus to bind to cells, and that aid its entry into a cell. As indicated, the lipid membrane is acquired when the virus is released from the cell by a process of budding from the plasma membrane, taking some of the plasma

EXHIBIT A

membrane with it. The budding process is reversed when the virus reinfects a cell.

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antisense RNA RNA molecules generated by reversing the orientation of the transcribed region of a gene with respect to a suitable transcriptional PROMOTER. This results in generating a transcript of the ANTISENSE DNA strand. Such antisense RNA has the potential to form an RNA–RNA duplex with the natural 'sense' mRNA transcript of the gene, thereby preventing its translation. Antisense RNA provides a means of inactivating the expression of specific genes and can be applied to both simple and complex eukaryotes. It has been exploited in genetic engineering: copies of antisense RNA genes have been engineered into the genome of, for example, tomato plants to prevent the production of enzymes that hasten softening of the fruit (*see* PLANT GENETIC ENGINEERING).

Green, P.J. et al. (1986) *Annu. Rev. Biochem.* **55**, 569–597.

antisense strand The strand in a DNA duplex complementary to the sense strand, and therefore corresponding to the sequence of the mRNA. It is also called the coding strand.

antitermination A mechanism utilized by both bacteriophage and bacterial species to regulate gene expression (*see* BACTERIAL GENE EXPRESSION). It involves the by-passing of a naturally occurring transcriptional terminator by RNA polymerase as a consequence of the enzyme interacting with one or more ancillary proteins (antitermination factors). Such termination readthrough results in an mRNA transcript with an extended 3′ sequence containing one or more CISTRONS which can now be translated. The best characterized example of antitermination is in the activation of expression of the delayed early genes of the bacteriophage LAMBDA during establishment of the lytic cycle. The antitermination factor involved is the pN protein, the product of the *N* gene. pN binds to two different sequences (*nutL* and *nutR*) located 5′ to the terminator to be read through and becomes attached to RNA polymerase as it transcribes through the *nutL* and *nutR* regions towards the transcriptional terminators t_{L1} and t_{R1}.

Friedman, D.I. et al. (1987) *Annu. Rev. Genet.* **21**, 453–488.

antithrombin *See*: BLOOD COAGULATION AND ITS DISORDERS; SERPINS.

antithrombin III deficiency Heritable condition involving the lack of the SERPIN proteinase inhibitor — ANTITHROMBIN III — which inhibits the enzymatic action of blood COAGULATION FACTORS, in particular activated Factors XII, XI, IX, X, plasmin, and thrombin. Both the binding of antithrombin III to the target enzymes and its inhibitory activity are increased many fold by HEPARIN. The condition is inherited as an AUTOSOMAL DOMINANT trait, and leads to a high risk of thromboembolism from early adult life onwards, presumably from the unopposed action of thrombin. *See*: BLOOD COAGULATION AND ITS DISORDERS.

α_1-antitrypsin A SERPIN synthesized by the liver and present in human serum. More than 30 allelic forms of α_1-antitrypsin have been distinguished in humans by acid starch gel electrophoresis or isoelectric focusing (*see* ELECTROPHORESIS). The locus is designated *Pi* (protease inhibitor). The most frequent alleles are of the M subtype (*PiM1*): two variants — Z and *S* — are associated with an appreciably reduced level of α_1-antitrypsin. No enzyme activity is detectable in homozygotes for the very rare NULL ALLELE *Pi0*.

The heritable disorder α_1-antitrypsin deficiency is a condition of variable outcome, inherited in an autosomal CODOMINANT fashion. 70–80% of homozygotes for the Z allele develop obstructive emphysema. Environmental factors, especially smoking, influence the manifestation of disease, possibly by stimulating release of proteinases from phagocytes. Liver disease usually first detected in childhood may progress to cirrhosis. The frequency of ZZ homozygotes is one in 3400 in the United Kingdom. PRENATAL DIAGNOSIS may be made by sampling foetal blood. The Z mutation results in an abnormality of secretion of α_1-antitrypsin (*see* SERPINS).

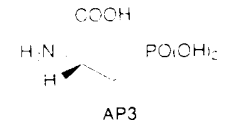
AP endonucleases A class of enzymes involved in DNA REPAIR in both prokaryotes and eukaryotes. These enzymes recognize depurinated or depyrimidinated residues in DNA and hydrolyse the phosphodiester bond at either the 5′ or 3′ side of the modified residue depending on the type of AP endonuclease. Cleavage of the phosphodiester bond permits access to an EXONUCLEASE which removes the residue immediately adjacent to the damaged residue thereby allowing resynthesis of the excised sequence.

AP lyase *See*: DNA REPAIR.

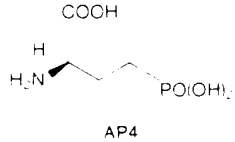
AP site APURINIC or APYRIMIDINIC SITE. *See also*: DNA REPAIR.

AP1 Eukaryotic TRANSCRIPTION FACTOR. *See*: EUKARYOTIC GENE EXPRESSION; STEROID RECEPTOR FAMILY.

AP3 (amino-3-phosphonopropanoate), AP4 (2-amino-4-phosphonobutanoate) Antagonists at both NMDA and metabotropic EXCITATORY AMINO ACID RECEPTORS.



AP3



AP4

AP5 (2-amino-5-phosphonopentanoic acid) Selective antagonist at the NMDA EXCITATORY AMINO ACID RECEPTOR.